Evaluation of Endometrial Receptivity by Ultrasound: Review Article

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Abstract:
Three-dimensional ultrasound (3D US) is a new imaging modality, which is being introduced into clinical practice. Although this technique will not probably replace two-dimensional ultrasound, it is being increasingly used. It has been reported that 3D US is a very high reproducible technique. The endometrium has been paid special attention when using this technique. The aim of this paper is to address some technical aspects of 3D US and to review critically its current status in evaluating endometrial function with special focus in its role in predicting pregnancy in assisted reproductive techniques. In spontaneous cycles endometrial volume grows during follicular phase remaining constant through the luteal phase. Endometrial vascularization increases during follicular phase peaking 2–3 days before ovulation, decreasing thereafter and increasing again during mid and late luteal phase. Data from studies analysing the role of 3D US for predicting IVF outcome are controversial. An explanation for these controversial findings might be different design of reported studies, specially the timing of ultrasound evaluation.
Keywords: Endometrial Receptivity, Ultrasound.

Tob Regul Sci. ™ 2023; 9(1): 5850 -5866
DOI: doi.org/10.18001 /TRS.9.1. 406

Introduction:

Endometrial receptivity and embryo quality are the two key factors for IVF success. To achieve a successful pregnancy, the embryo must implant and establish a connection to the maternal circulation. This process requires the endometrium to be receptive **(1).**

The endometrium changes throughout a normal menstrual cycle under the influence of ovarian hormones, such as estrogen secreted by the growing follicles and progesterone (P) secreted later by the luteal corpus **(2).**

Endometrial receptivity means that the endometrium has reached a mature stage in which it is completely ready to accept the implanting embryo. It corresponds to the window of implantation (WOI), which lasts for 3–6 days within the endometrial secretory phase. Under certain circumstances, such as the presence of inflammation or uterine structural anomalies, the WOI could be shortened or displaced throughout the menstrual cycle, which would prevent proper implantation. Such conditions most often result in infertility and/or pregnancy loss **(3).**

Endometrial receptivity and selectivity are two complementary concepts introduced to describe the endometrium as a biosensor of embryo quality **(4).** However, even with the latest modern technology for chromosome screening, manuscripts recently published show an ongoing pregnancy rate with euploid embryo transfer of about 45% for a general infertility population **(5).**

In recent years, several methods have been used to assess endometrial receptivity, including:

1) Ultrasound,
2) Hysteroscopy
3) Expression Of Related Molecules in Endometrial Tissue
4) Uterine Fluid examination **(6).**

1) Endometrial Receptivity Markers Evaluated by Ultrasound:

Ultrasound is a convenient and non-invasive method used for the evaluation of the endometrium during IVF cycles **(7).** The addition of three-dimensional (3D) US has further enhanced the application of conventional 2D US, offering many practical applications and clinical advantages within this context **(8).**

Endometrial assessment has become part of standard monitoring during ICSI-ET. The endometrial characteristics, including endometrial pattern, endometrial blood flow, and endometrial thickness (EMT) have been regarded as prognostic factors of IVF–ICSI treatment **(7).**

A) Endometrial thickness:

Although it remains a controversial issue, endometrial thickness (EMT) is the most widely used prognostic factor for endometrial receptivity during assisted reproductive techniques **(9).** As the sonographic assessment of EMT is simple and non-invasive, EMT on the hCG day is adopted as a marker to evaluate the endometrial receptivity of IVF-ET patients. However, findings on the association between EMT and pregnancy success are inconsistent. It has been found that too thin or too thick endometrium has an adverse effect on IVF-ET outcomes **(10).**

Endometrial thickness is measured as the maximal echogenic distance between the junction of the endometrium and myometrium in the mid-sagittal plane **(11).** When intracavitary fluid is present, endometrial thickness is measured by adding both layers together. When intracavitary pathology is present measure total EMT including the lesion unless it is a well-defined myoma that can be measured separately **(12).**

A preovulatory endometrial thickness of 7 mm or more is the cutoff for endometrial receptivity, below which many physicians would cancel an embryo transfer **(13).** The definition of a thin endometrium varies between studies but is defined as <7 or <8 mm on the day of ovulation trigger in fresh IVF cycles and before the start of progesterone in frozen–thaw embryo transfer (ET) cycles **(14).**

It is also reported that a high clinical pregnancy rate could be obtained when EMT is 9mm **(15).** Furthermore, the clinical pregnancy rate is found to be significantly reduced and the spontaneous abortion rate is elevated if EMT is 14 mm. On the contrary, another observational study suggests that there is no adverse pregnancy outcome when EMT reaches 14 mm **(13).**

Specialists have the option of cryopreserving embryos if the endometrial thickness is found to be unsuitable for embryo transfer and transferring the embryo to the uterine cavity at a later stage in a frozen–thawed cycle, which may be natural or hormonally controlled. The National Institute of Health and Care Excellence guidelines advise avoiding the transfer of embryos into a uterine cavity with an endometrium of less than 5 mm thickness as pregnancies are rare with very thin endometrium **(16).**

However, the exact influence of EMT on the day of hCG administration on pregnancy outcomes remains debated due to a lack of large-scale systemic studies.

B) Endometrial Pattern:

The endometrial pattern reflects the anatomical changes associated with the menstrual cycle following progestin exposure and can be used to track the pre- and peri-implantation uterine environment **(17).** It is used as a marker of endometrial receptivity **(18).**

Ahmadi et al., (19) described the endometrial pattern as one of the following three categories, patterns A, B, and C:

- ✓ Pattern A with a triple line was characterized as hypoechoic endometrium with well-defined hyperechoic outer walls and a central echogenic line.
- ✓ Pattern B was described as an isoechoic endometrium with poorly defined outer walls and a non-prominent central echogenic line.
- ✓ Pattern C was defined as homogeneous hyperechoic endometrium.

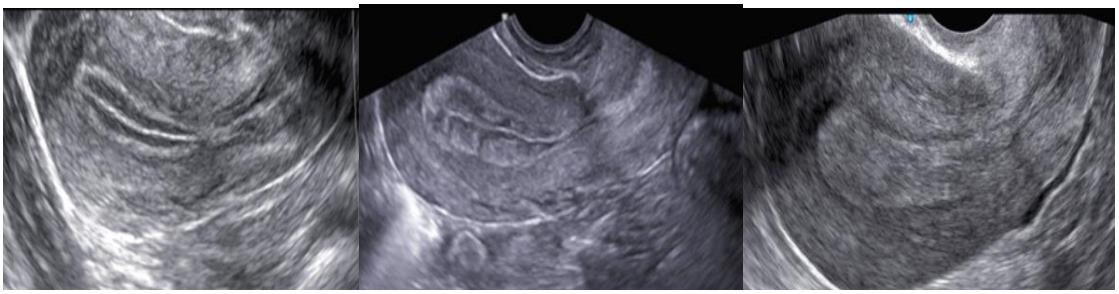

Figure (1) Triple line (A), Heterogeneous-echogenic (B), Homogeneous-echogenic pattern (C) (19).

During an ART treatment cycle, the most prevalent endometrial pattern observed before embryo transfer is a trilinear endometrial pattern **(20)** While some studies have failed to observe an association between endometrial pattern and pregnancy outcome **(21),** others reported a negative correlation between a mid-late secretory (homogeneous, hyperechoic) endometrium and pregnancy outcome (**22)**

These mixed results may be due to the small sample size of most studies with limited precision and reduced statistical power to detect associations **(19).**

C) Endometrial Compaction:

The focus of endometrial sonographic evaluation during an IVF cycle is on the endometrial pattern and thickness before triggering the final stage of oocyte maturation **(23).**

It is hypothesized that the change in endometrial thickness between the end of the estrogen phase and the time of embryo transfer may be more important to predict pregnancy outcome than measuring endometrial thickness at the time of embryo transfer. Specifically, it was hypothesized that the endometrial thickness should decrease in the natural or artificial luteal phase as the endometrium becomes denser (hyperechoic on ultrasound) because of the secretory changes that are induced by progesterone **(24)**

A significant increase in ongoing pregnancy was found if the endometrium decreased in thickness between the end of the estrogen phase and the day of ET in hormonally replaced frozen ET (FET) cycles. This decrease in thickness is termed 'compaction.' **(25).**

The endometrial compaction is calculated by the delta of the endometrial thickness between the end of the estrogen phase and the day of ET. Also, it is noticed that an increase in ongoing pregnancy

rates with each quartile increases in the change of endometrial thickness. That is, the greater the degree of compaction, the higher the ongoing pregnancy rate **(24).**

An explanation for the lack of endometrial compaction may be the presence of progesterone receptor deficiency or resistance in the endometrium of some infertile women. Numerous etiologic factors have been proposed for progesterone receptor resistance, including overexpression of BCL-6 and SIRT-1 **(26),** chronic endometrial inflammation, progesterone receptor gene polymorphisms, altered microRNA expression, and epigenetic modifications to progesterone receptors **(27).**

D) Uterine Junctional Zone:

The junctional zone has gained considerable interest in the ART setting in the last few years **(28).** It represents a distinct layer of the inner myometrium and envelops the entire endometrial cavity. Interestingly, unlike the outer myometrium, which is thought to be mesenchymal in origin, the inner myometrium along with the junctional zone is derived from the embryonic paramesonephric ducts, from which the endometrium also arises **(29).**

This is thought to result in its characteristic hypoechoic appearance in Ultrasound. The role of the junctional zone in implantation and pregnancy is likely to be multifactorial. For example, myometrial contractions have been shown to originate exclusively from the junctional zone **(28).**

Although the JZ can often be visualized on 2D ultrasound, the acquisition of a 3D volume enables a more complete assessment of the sagittal, transverse, and coronal planes, as shown in a standardized multiplanar view, figure 2 **(30).**

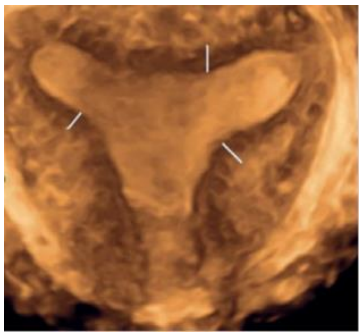

figure (2) Three-dimensional rendered view of the uterus in the coronal plane showing the junctional zone as a hypoechoic area surrounding the endometrium.

Imaging of the JZ may be optimized by using a post-processing rendering mode, The JZ may be reported as regular, irregular, interrupted, not visible, or not assessable or may manifest more than one feature (e.g., irregular, and interrupted) **(12).** If the JZ is ill-defined or not visible, it should be reported

as 'non-measurable.' The magnitude and extent of any irregularity of the JZ may be reported and its JZ location (anterior, posterior, lateral left, lateral right, fundus) specified according to the research protocol. The magnitude of a JZ irregularity is expressed as the difference between the maximum and minimum JZ thickness: (JZdif) = JZmax – JZmin **(31).**

The thickening of JZ was found to have a negative correlation with implantation following intracytoplasmic sperm injection (ICSI), with an almost 90% failure rate in patients with a JZ thickness of >10mm **(32)**

These findings suggest that the JZ may affect the implantation of an embryo and the outcome of pregnancy. This was also highlighted by **(33)** who found that following IVF, women with unsuccessful pregnancies had a thicker JZ (6.75 mm) compared to women with successful pregnancies (5.14 mm) there was a 95.8% implantation rate failure in patients with JZ of 7–10 mm. **(34).**

E) Uterine Peristalsis:

In the non-pregnant uterus, uterine contractions originate from the JZ and are visualized as wave-like movements. JZ is a hormone-dependent structure, uterine peristalsis is therefore controlled by estradiol and progesterone in the normal uterus; these wave-like contractions have a cycle-dependent direction from the cervix to the fundus during the follicular phase and from the fundus to the cervix during the luteal phase. The contraction frequency and amplitude increase as the menstrual cycle moves towards ovulation, under the influence of progesterone (**35**).

During post-ovulation, there is a decrease in the frequency of uterine contractions **(36).** These properties were found to aid in menstrual shedding **(35),** as well as in the journey of sperm towards the Fallopian tube. In early pregnancy, the pattern of contraction assists in the implantation of the blastocyst and in optimizing oxygen and nutrient supply to the decidua **(37).**

After IVF, the transferred embryo often migrates within the uterine cavity before implantation **(38)**. Low-frequency Uterine Contractions at the time of ET, mediated by appropriate exposure to Progesterone or delayed transfer at the blastocyst stage have been associated with higher implantation rates after IVF **(39),** Conversely, traumatic transfer trans myometrial or use of tenaculum, generates Uterine Contractions and can impair implantation **(40).** Clinical pregnancy rate (CPR). Hence, relative uterine quiescence appears required for successful implantation after IVF **(41).**

Alterations in the pattern of JZ contractions may contribute to reproductive disorders and adverse pregnancy outcomes. High-frequency uterine contractions prior to embryo transfer in the process of IVF were found to decrease rates of successful pregnancies. Pregnancy loss was speculated to be due to

abnormal contractility of the JZ **(42).** The JZ contraction may play a role in higher rates of ectopic and heterotopic pregnancy rates after an embryo transfer in IVF **(36).**

Sub-endometrial contractility monitoring is not routinely performed in most IVF units; it is certainly a tool that can be considered in cases of repeated implantation failure, in patients reporting cramps around the planned time of the embryo transfer, or as a reassuring modality to assess the uterus during preparations for embryo transfer **(43).**

F) Uterine Blood Flow:

❖ **Uterine Artery Doppler:**

Adequate blood flow in the uterus is important for good endometrial growth and increased endometrial receptivity **(44).** Many studies concluded that decreased uterine artery blood flow and endometrial perfusion could be crucial factors for the diagnosis of unexplained infertility, abortion, and in vitro fertilization (IVF) failure **(45).**

Normally at the mid-luteal phase, the endometrium changes from proliferative to secretory phase, the blood supply of the uterus is increased, uterine artery impedance is decreased and so receptivity of the uterine endometrium increases **(46).** Normally, the endometrial perfusion and blood flow of the uterine artery improve significantly during the luteal phase of the menstrual cycle; therefore, the use of uterine artery Doppler and measuring the uterine arterial impedance could evaluate the endometrial receptivity **(47).**

The most common Doppler indices used for the assessment of uterine artery blood flow impedance are the resistance index (RI), the pulsatility index (PI), and the systolic/diastolic (S/D) ratio **(48).** Increased impedance of uterine arteries' blood flow leads to poor growth of endometrium and endometrial thinning **(49).**

It is found that pulsatility indexes (between 2.5 and 3.6) have been associated with poor reproductive success **(50).** Also, it was assumed that women with unexplained infertility had higher uterine artery impedance than that of normal fertile women so decreased uterine artery blood flow and uterine perfusion could be a cause of unexplained infertility **(51).**

❖ **Sub-Endometrial, Endometrial Blood Flow:**

The quality of the endometrium as well as the sub-endometrial perfusion and vascularization may be more important than the global flow throughout the uterus, quantitative assessment of spiral artery blood flow and vessel density may allow further insight into endometrial receptivity **(52).**

Endometrial sub-endometrial blood flow distribution pattern assessed by transvaginal color Doppler before ET was correlated with the implantation and PR of IVF treatment **(53).**

The zones of vascularity are classified into:

- ✓ Zone 1: the vascularity on power Doppler is seen only at the endometrium myometrium junction.
- ✓ Zone 2: vessels penetrate through the hyperechogenic endometrial edge.
- ✓ Zone 3: vascularity reaches intervening hypoechogenic.
- ✓ Zone 4: vascularity reaches the endometrial cavity **(54)**

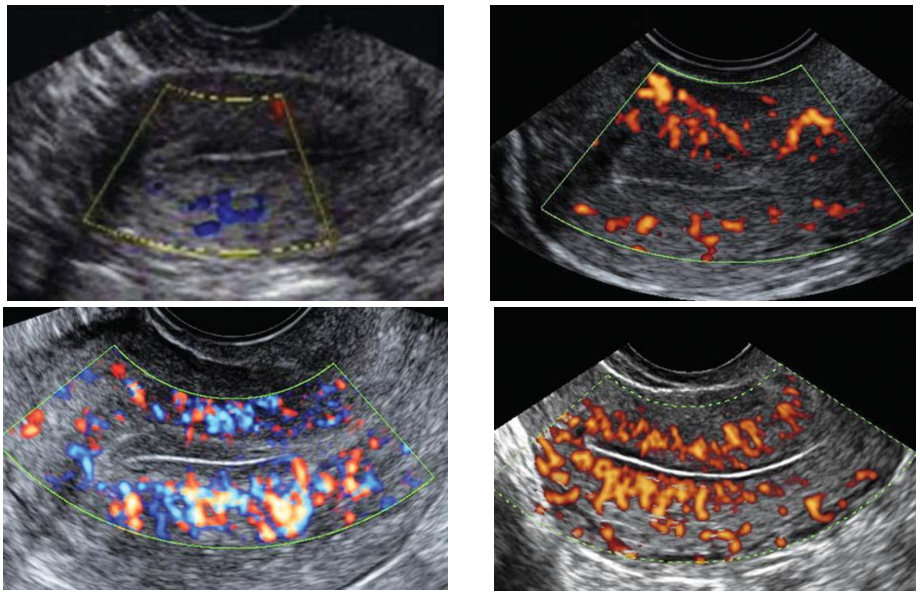

Figure (3) Endometrial vascularity: Zone 1, Zone 2: Zone 3, Zone 4 (55)

Conception rates were almost double when endometrial vascularity was seen in zones 3 and 4 than when the vascularity in the endometrium reached only zones 1 and 2. The abortion rates also are high when the vascularity in the endometrium reaches only zones 1 and 2. **(55).**

❖ **The 3D color flow (VOCAL):**

Color flow within a lesion may be quantified using 3D ultrasound with virtual organ computer-aided analysis (VOCAL) **(56).** However, 3D US vascularization indices can be affected by trivial factors, such as the US machine setting and speed of 3D volume acquisition **(57).**

Three-dimensional (3D) ultrasonography in combination with power Doppler (3D-PD), a noninvasive tool to evaluate the blood supply in the endometrium and the sub-endometrial regions has been used to indicate endometrial receptivity and pregnancy outcome **(58).**

G) Endometrial Volume:

Accurate volume measurement has been possible only after the introduction of 3-dimensional (3D) ultrasonography, virtual semiautomatic organ calculation (virtual organ computer-aided analysis [VOCAL]), and automatic volume calculation (AVC). With the use of these modes, it is possible to generate a 3D model of the endometrium **(59).**

Several studies attempted to correlate the endometrial volume with the pregnancy outcome following ART, with conflicting results. Some studies found a significantly increased endometrial volume in women achieving a pregnancy following ART **(60),** Whereas another study showed no significant association between endometrial volume and clinical pregnancy outcome **(61)**

Other studies tried to determine certain thresholds for endometrial volume required to achieve a pregnancy. Some of these reported significantly reduced pregnancy rates with endometrial volumes of less than 2 ml **(62),** while other study reported clinical pregnancy rate increased following IVF with frozen–thawed embryo transfer based on the cut-off of 3.2 mL for endometrial volume as measured on the day of the embryo transfer, the sensitivity was 80% and the specificity was 77.1% **(63).**

2) Hysteroscopic Evaluation of endometrial receptivity:

The mid-luteal endometrium was classified as 'good' based on the ring-type aspect of the glandular openings and the presence of well-developed varicose-like vessels during hysteroscopic assessment **(64).** Pregnancy outcomes following the assessment of endometrial receptivity by hysteroscopy in the mid-luteal phase of a natural cycle pregnancy rate was higher in women with 'good' endometrium compared to women with 'poor' endometrium **(65).**

Another way to assess endometrial receptivity for implantation has been conducted by using hysterofiberscopically laser blood-flowmetry to measure endometrial tissue blood flow **(66).**

3) Expression Of Related Molecules in Endometrial Tissue

Historically, endometrial histology was used as the primary indicator of endometrial receptivity **(67).** Decreased cyclin E in the endometrial function test reflects the absence of estrogen receptor activity and is a marker of endometrial receptivity. In some infertile women, estrogen receptors remain present, or their downregulation is delayed. Both situations could represent progesterone resistance, which is one of the principal areas of research into receptivity markers. **(68).**

Endometrial biopsy with assessment of Bcl-6 and SIRT-1 expression has been proposed as a test to determine the likelihood of endometriosis or implantation failure in unexplained infertility because of progesterone resistance (**69**).

Of interest, medical suppression with the use of a GnRH agonist or surgical treatment of endometriosis normalized Bcl-6 expression in the endometrium and improved pregnancy outcomes in these women (**70**). Quantifying endometrial receptivity by endometrial biopsy postpones the completion of fertility treatment due to the invasiveness of the procedure (**71**).

Endometrial Receptivity Array (ERA):

A recent development in the assessment of the WOI is a multigene microarray together with bioinformatics that has been proposed to identify genetic alterations associated with endometrial receptivity in an endometrial biopsy. The endometrial receptivity array (ERA) is an attempt to clinically improve histologic detection of embryonic–endometrial dyssynchrony due to accelerated or delayed endometrial luteal-phase differentiation (**72**).

The endometrial receptivity array (ERA) test examines the expression of 238 genes thought to be involved in implantation. The goal of this test is to enable customized FET based on the determination of a personalized WOI. In a mock cycle, an endometrial biopsy is performed on the seventh day after an LH surge or on the sixth day of progesterone during a hormone replacement (HRT) cycle. Results are expressed as pre-receptive, receptive, or post-receptive. If the result is nonreceptive, for example, pre-receptive, the embryo replacement timing is delayed in a subsequent cycle, thereby enabling personalized embryo transfer (**73**).

The problems with endometrial biopsy tests such as histologic dating, the ERA test, Bcl-6 and SIRT-1 measurement, and the endometrial function test are that they are invasive, and the results need to be extrapolated to a subsequent cycle in which the embryo transfer will occur. This brings us back to ultrasound, which is non-invasive and can be used in the cycle of interest (**71**).

Most recently, a 2022 RCT by Doyle et al. evaluated live birth after standard vs. ERA-timed euploid embryo transfer and found no difference in the live birth rates. (**74**).

4) Uterine Fluid examination

Uterine fluids are an important medium of communication between the embryo and endometrium it includes an admixture of endometrial secretions, plasma transudates, and oviductal

fluid **(75).** The uterine fluid contains extracellular vesicles, RNAs, DNAs, regulatory proteins, ions, lipids, and other bioactive factors that play a significant role in embryo implantation **(76).**

Thus, the examination of uterine fluid provides an opportunity to find noninvasive biomarkers of endometrial receptivity for clinical use. Also, the aspiration of uterine fluid before embryo transfer does not affect the embryo implantation rate **(77).**

The technique of uterine aspiration is by insertion of an ET catheter through the cervix to a depth of 4cm from the external cervical os, the inner catheter was introduced into the uterine cavity to a point 1–2cm from the uterine fundus to avoid contamination with cervical mucus. A 2.5 mL syringe was connected to the inner catheter, and suction was applied. Approximately 5–10μL of uterine fluid obtained was immediately placed into 20μL of RNA-later buffer. **(78).**

Uterine lavage offers a higher percentage of data interpretation than pipelle biopsy, as the fluid washes away and incorporates substances from the endometrial glycocalyx. (**79).** Furthermore, endometrial fluid aspirate analysis correlates with endometrial biopsy results **(80).**

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